

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

*In re* application of:

HORWITZ, David A.

Serial No.: To Be Assigned

Filing Date: August 27, 2003

For: *USE OF CYTOKINES AND  
MITOGENS TO INHIBIT  
PATHOLOGICAL IMMUNE  
RESPONSES*

Examiner: To Be Assigned

Art Unit: 1654

"EXPRESS MAIL" LABEL NO. **EV 298966277 US**

DATE OF DEPOSIT August 27, 2003

This Information Disclosure Statement and Substitute PTO/SB/8A-B are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to: Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

**INFORMATION DISCLOSURE STATEMENT**

Mail Stop Patent Application  
Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

Sir:

In satisfaction of the duty of disclosure under 37 C.F.R. § 1.56, and in accordance with the provisions of 37 C.F.R. §§ 1.97 and 1.98, Applicants wish to draw the attention of the U.S. Patent and Trademark Office to the references cited on the accompanying substitute PTO/SB/8A-B, substitute for form PTO-1449. Since copies of these references were provided either by Applicants or the Examiner in the following related U.S. Applications – Serial No. 10/028,944, filed December 21, 2001 (pending) – upon which the instant application relies for its priority date, in accordance with 37 C.F.R. § 1.98(d), no copies of these references are enclosed.

Serial No.: To Be Assigned  
Filing Date: August 27, 2003

None of the foregoing references is believed to disclose the invention as claimed.

Nothing herein shall constitute an admission concerning the contents of any of the cited references, nor shall the inclusion of a reference herein be considered an admission that the reference constitutes prior art against the invention claimed in the above-identified application. Submission of the present document shall not be construed as an admission that a search has been made or that better art does not exist.

This Information Disclosure Statement is being filed concurrently with the filing of a national application and therefore no fee is required. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,  
DORSEY & WHITNEY LLP

Dated: 8/27/03  
Dorsey & Whitney LLP  
Intellectual Property Department  
Four Embarcadero Center, Suite 3400  
San Francisco, CA 94111-4187  
Telephone: (415) 781-1989  
Facsimile: (415) 398-3249

BY: 

Renee M. Kossak, Reg. No. 47,717 for  
Richard F. Trecartin, Reg. No. 31,801

Customer Number: **32940**

Attachments:  
Form PTO/SB/8A-B, Substitute for form PTO 1449

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				<b>Complete if Known</b>	
				Application Number	To Be Assigned
				Filing Date	Herewith
				First Named Inventor	HORWITZ, David A.
				Group Art Unit	
				Examiner Name	
Sheet	1	of	8	Attorney Docket Number	A-67279-8/RFT/RMS/RMK (469443-63)

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.	U.S. Patent Document Number-Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	6,447,765 B1	09-2002	Horwitz	
	A2	6,406,696 B1	06-2002	Bluestone	
	A3	6,358,506 B1	03-2002	Horwitz	
	A4	6,228,359 B1	05-2001	Horwitz	
	A5				
	A6				
	A7				
	A8				
	A9				
	A10				
	A11				

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.	Foreign Patent Document Country Code <sup>2</sup> Number <sup>4</sup> Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
	B1	WO 93/17698 A1	09-1993	Schering Corp.		
	B2	WO 97/42324 A1	11-1997	Schering Corp.		
	B3	WO 99/25366 A1	05-1999	Horwitz		
	B4	WO 99/48524 A1	09-1999	Horwitz		
	B5	WO 00/66158 A3	11-2000	Horwitz		
	B6	WO 01/16296 A2	03/2001	Horwitz		
	B7	WO 01/77299 A2	10-18-2001	Horwitz		

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS					
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.			
	C1	ANASETTI et al., "Treatment of acute graft-versus-host disease with a nonmitogenic anti-CD3 monoclonal antibody", Transplantation 54:844-851 (1992)			
	C2	ASAI O, et al., "Suppression of graft-versus-host disease and amplification of graft-versus-tumor effects by activated natural killer cells after allogeneic bone marrow transplantation," Journal of Clinical Investigation 101(9):1835-1842 (1998)			
	C3	ASANO M, et al., "Autoimmune disease as a consequence of developmental abnormality of a T cell subpopulation." J Exp Med. 1996 Aug 1;184(2):387-96.			
	C4	AUCHINCLOSS, Hugh Jr., et al, in Fundamental Immunology 4th Ed., Paul, W.E. (ed.) Lippincott-Raven: Philadelphia, New York; 1999 pp. 1182-1222.			

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1118358\_1.DOC

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				<b>Complete if Known</b>	
				Application Number	To Be Assigned
				Filing Date	Herewith
				First Named Inventor	HORWITZ, David A.
				Group Art Unit	
				Examiner Name	
Sheet	2	of	8	Attorney Docket Number	A-67279-8/RFT/RMS/RMK (469443-63)

**OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS**

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	†
	C5	BARKER et al., "Identification of multiple and distinct CD8+ T cell suppressor activities: dichotomy between infected and uninfected individuals, evolution with progression of disease, and sensitivity to gamma irradiation," J Immunol 156:4476-4483 (1996)	
	C6	BETZ, M. and FOX, B.S., "Prostaglandin E2 inhibits production of Th1 lymphokines but not of Th2 lymphokines," J Immunol. 1991 Jan 1;146(1):108-13.	
	C7	BLAZAR et al., "Both CD4+ and CD8+ T Cells Can Cause Accelerated GVHD Lethality in the Presence of High In Vivo Doses of Exogenous IL10: Role of Interferon Gamma (IFN ) in GVHD Induction," Blood 88:247 (1996) (abstract)	
	C8	BLAZAR et al., "FK506 inhibits graft-versus-host disease and bone marrow graft rejection in murine recipients of MHC disparate donor grafts by interfering with mature peripheral T cell expansion post-transplantation", J. Immunol 153:1836-1846 (1994)	
	C9	BLAZAR et al., "Murine recipients of fully mismatched donor marrow are protected from lethal graft-versus-host disease by the in vivo administration of rapamycin but develop an autoimmune-like syndrome", J. Immunol 151:5726-5741 (1993)	
	C10	BLAZAR et al., "Recent advances in graft-versus-host disease (GVHD)", Immunol Rev 157:79-90 (1997)	
	C11	BONIG H, et al., "Transforming growth factor-beta1 suppresses interleukin-15-mediated interferon-gamma production in human T lymphocytes." Scand J Immunol. 1999 Dec;50(6):612-8.	
	C12	BONINI et al., "HSY-TK gene transfer into donor lymphocytes for control of allogeneic graft-versus-leukemia, Science 276:1719-1724 (1997)	
	C13	BORDER et al., "Transforming growth factor-beta in disease: the dark side of tissue repair," J Clin Invest 90:1-7 (1992)	
	C14	BOUSSIOTIS et al., "B7 but not intercellular adhesion molecule-1 costimulation prevents the induction of human alloantigen-specific tolerance," J Exp Med 178:1753-1763 (1993)	
	C15	BOUSSIOTIS, "Altered T-cell receptor + CD28-mediated signaling and blocked cell cycle progression in interleukin 10 and transforming growth factor- treated alloreactive T cells that do not induce graft-versus-host disease," Blood 97:565-571 (2001)	
	C16	BUCY, R.P. et al., FASEB J. 1995 9:A497 (Abstract)	
	C17	CHANDRASEKAR, B., et al., "Dietary calorie restriction inhibits transforming growth factor-beta (TGF- beta) expression in murine lupus nephritis", 9th International Congress on Immunology, 848 (1995) (Abstract)	
	C18	CHAVIN, et al., "Anti-CD2 mAbs Suppress Cytotoxic Lymphocyte Activity by the Generation of Th2 Suppressor Cells and Receptor Blockade," J Immunol 152:3729-3739 (1994)	
	C19	CHEN W, et al., "T cells specific for a polymorphic segment of CD45 induce graft-versus-host disease with predominant pulmonary vasculitis." J Immunol. 1998 Jul 15;161(2):909-18.	
	C20	CHONG P. et al. "Inhibition of protein-kinase C in peripheral blood mononuclear cells of patients with systemic lupus erythematosus: effect on spontaneous immunoglobulin production," Autoimmunity, 10:227-231 (1991)	
	C21	COSIMI, A.B., et al., "Treatment of acute renal allograft rejection with OKT3 monoclonal antibody," Transplantation. 1981 Dec;32(6):535-9.	
	C22	DELGIUDICE, G., et al., "TGF-beta activity is increased in systemic lupus erythematosus (SLE) and progressive systemic sclerosis (PSS)", Arthritis and Rheumatism Vol. 36 (9 Suppl.) p S196(Sept. 1993)	

Examiner Signature	Date Considered
--------------------	-----------------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible.

<sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1118358\_1.DOC

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				<b>Complete if Known</b>	
				Application Number	To B Assigned
				Filing Date	H rewith
				First Named Inventor	HORWITZ, David A.
				Group Art Unit	
				Examiner Name	
Sheet	3	of	8	Attorney Docket Number	A-67279-8/RFT/RMS/RMK (469443-63)

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS					
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.			
	C23	DOOMS, H. et al., "IL-2 and IL-15 direct the outcome of inappropriate CD4+ T cell stimulation towards apoptosis and anergy respectively," European Cytokine Network, 9(3):169 (1998)			
	C24	DUMONT et al., "Distinct Mechanisms of Suppression of Murine T Cell Activation by the Related macrolides FK-506 and Rapamycin", J. Immunol 144:251-258 (1990)			
	C25	DUPONT, B., "Immunology of hematopoietic stem cell transplantation: a brief review of its history", Immunol Reviews 157:5-12 (1997)			
	C26	EARLY E, and Reen DJ. "Rapid conversion of naive to effector T cell function counteracts diminished primary human newborn T cell responses." Clin Exp Immunol. 1999 Jun;116(3):527-33. (Abstract)			
	C27	FAST, "Generation and characterization of IL-2-activated veto cells", J Immunol 149:1510-1515 (1992)			
	C28	FERNANDES, G., et al., "Calorie restriction delays autoimmune murine lupus by differentially modulating oncogenes and TGF- beta-1 expression", 9th International Congress on Immunology., 848 (1995).(Abstract)			
	C29	FOWLER et al., "Donor CD4-enriched cells of Th2 cytokine phenotype regulate graft-versus-host disease without impairing allogeneic engraftment in sublethally irradiated mice", Blood 84:3540-3549 (1994)			
	C30	GAO Q, et al., "CD4+CD25+ cells regulate CD8 cell anergy in neonatal tolerant mice." Transplantation. 1999 Dec 27;68(12):1891-7.			
	C31	GARDERET L, et al., "Effective depletion of alloreactive lymphocytes from peripheral blood mononuclear cell preparations." Transplantation. 1999 Jan 15;67(1):124-30.			
	C32	GOLDMAN et al., "Bone marrow transplantation for chronic myelogenous leukemia in chronic phase. Increased risk for relapse associated with T-cell depletion", Ann Intern Med 108:806-814 (1988)			
	C33	GRATAMA et al., "Treatment of Acute Graft-Versus-Host Disease With Monoclonal Antibody OKT3. Clinical results and effect on circulating T lymphocytes", Transplantation 38(5):469-474 (1984)			
	C34	GRAY et al., "The role of transforming growth factor beta in the generation of suppression: an interaction between CD8+ T and NK cells", J Exp Med 180:1937-1942 (1994)			
	C35	GRAY et al., "Activated Natural Killer Cells Can Induce Resting B Cells to Produce Immunoglobulin," Arthritis & Rheumatism, 37(9)suppl:S378 (1994)			
	C36	GRAY, J. D., et al., "Generation of an Inhibitory Circuit Involving CD8+ T Cells, IL-2, and NK Cell-Derived TGF-beta: Contrasting Effects of Anti-CD2 and Anti-CD3", J Immunol., 160:2248-2254 (1998).			
	C37	GRIBBEN et al., "Complete blockade of B7 family-mediated costimulation is necessary to induce human alloantigen-specific anergy: a method to ameliorate graft-versus-host disease and extend the donor pool", Blood 97:4887-4893 (1996)			
	C38	GROUX, H., et al., "A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis," Nature. 1997 Oct 16;389(6652):737-42.			
	C39	HAHN, B.H., Dubois Lupus Erythematosus, 5th Ed. (1997), pp. 69-76 (D.J. Wallace et al. eds., Williams and Wilkins, Baltimore)			
	C40	HALVERSON, et al., "In Vitro Generation of Allospecific Human CD8+ T Cells of Tc1 and Tc2 Phenotype," Blood 90(5):2089-2096 (1997)			
	C41	HAN, et al., "A New Type of CD4+ Suppressor T cell Completely Prevents Spontaneous Autoimmune Diabetes and Recurrent Diabetes in Syngeneic Islet-Transplanted NOD Mice," Journal of Autoimmunity, 9:331-339 (1996)			

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1118358\_1.DOC

Substitute for form 1449A/PTO (Modified)  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				<b>Complete if Known</b>	
				Application Number	To B Assign d
				Filing Date	Herewith
				First Named Inventor	HORWITZ, David A.
				Group Art Unit	
				Examiner Name	
Sheet	4	of	8	Attorney Docket Number	A-67279-8/RFT/RMS/RMK (469443-63)

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS					
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.			T <sup>6</sup>
	C42	HEITGER A, et al. "Essential role of the thymus to reconstitute naive (CD45RA+) T-helper cells after human allogeneic bone marrow transplantation." Blood. 1997 Jul 15;90(2):850-7.			
	C43	HERVE et al., "Treatment of Corticosteroid Resistant Acute Graft-Versus-Host Disease by In Vivo Administration of Anti-Interleukin-2 Receptor Monoclonal Antibody (B-B10)", Blood 75(4):1017-1023 (1990)			
	C44	HIROHATA et al., "Role of IL-2 in the generation of CD4+ suppressors of human B cell responsiveness", J Immunol 142:3104-3112 (1989)			
	C45	HIROKAWA et al., "Human resting B lymphocytes can serve as accessory cells for anti-CD2-induced T cell activation", J. Immunol. 149:1859-1866, 1992			
	C46	HIRUMA et al., "Effects of anti-CD3 monoclonal antibody on engraftment of T-cell-depleted bone marrow allografts in mice: host T-cell suppression, growth factors, and space", Blood 79:3050-3058 (1992)			
	C47	HORWITZ DA, et al., "Decreased production of interleukin-12 and other Th1-type cytokines in patients with recent-onset systemic lupus erythematosus." Arthritis Rheum. 1998 May;41(5):838-44.			
	C48	HORWITZ, D. A., et al., "The immunoregulatory effects of NK cells: the role of TGF- $\beta$ and implications for autoimmunity", Immunology Today, Vol. 18(11):538-542 (Nov. 1997).			
	C49	HORWITZ, D.A., Dubois' Lupus Erythematosus, 5th Ed. (1997), pp. 155-194 (D.J. Wallace et al. eds., Williams and Wilkins, Baltimore)			
	C50	HUGGINS, M. L., et al., "Modulation of the Autoimmune Response in Lupus Mice by Oral Administration of Attenuated Salmonella typhimurium Expressing the IL-2 and TGF- $\beta$ Genes", Annals of New York Acad. of Sciences, Vol. 815:499-502 (1997)			
	C51	JACKSON AL, et al., "Restricted expression of p55 interleukin 2 receptor (CD25) on normal T cells." Clin Immunol Immunopathol. 1990 Jan;54(1):126-33.			
	C52	JONULEIT, H., et al., "Induction of interleukin 10-producing, nonproliferating CD4(+) T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells," J Exp Med. 2000 Nov 6;192(9):1213-22.			
	C53	KANEGANE H, et al., "A novel subpopulation of CD45RA+ CD4+ T cells expressing IL-2 receptor alpha-chain (CD25) and having a functionally transitional nature into memory cells." Int Immunol. 1991 Dec;3(12):1349-56.			
	C54	KINTER et al., "Interleukin 2 induces CD8+ T cell-mediated suppression of human immunodeficiency virus replication in CD4+ T cells and this effect overrides its ability to stimulate virus expression", Proc. Natl. Acad. Sci. USA 92:10985-10989 (1995)			
	C55	KIRK, A.D., et al., "CTLA4-Ig and anti-CD40 ligand prevent renal allograft rejection in primates," Proc Natl Acad Sci U S A. 1997 Aug 5;94(16):8789-94.			
	C56	KLINMAN DM, et al., "Quantitation of IgM- and IgG-secreting B cells in the peripheral blood of patients with systemic lupus erythematosus." Arthritis Rheum. 1991 Nov;34(11):1404-10.			
	C57	KOH et al., "Adoptive cellular immunotherapy: NK cells and bone marrow transplantation," Histol Histopathol 15:1201-1210 (2000)			
	C58	KOIDE, J. and ENGLEMAN, E.G., "Differences in surface phenotype and mechanism of action between alloantigen-specific CD8+ cytotoxic and suppressor T cell clones," J Immunol. 1990 Jan 1;144(1):32-40.			
	C59	KRENGER et al., "Effects of exogenous interleukin-10 in a murine model of graft-versus-host disease to minor histocompatibility antigens", Transplantation 58:1251-1257 (1994)			

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible.

<sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1118358\_1.DOC

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)				<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				Application Number	To B Assign d
				Filing Date	H r with
				First Named Inventor	HORWITZ, David A.
				Group Art Unit	
				Examiner Name	
Sheet	5	of	8	Attorney Docket Number	A-67279-8/RFT/RMS/RMK (469443-63)

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS					
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.			
	C60	KRENGER et al., "Polarized type 2 alloreactive CD4+ and CD8+ donor T cells fail to induce experimental acute graft-versus-host disease", J Immunol 153:585-593 (1995)			
	C61	LANCASTER, F., et al., "Anti-idiotypic T cells suppress rejection of renal allografts in rats," Nature. 1985 May 23-29;315(6017):336-7.			
	C62	LANGREHR, J.M., et al., "Evidence that nitric oxide production by in vivo allosensitized cells inhibits the development of allospecific CTL," Transplantation. 1992 Mar;53(3):632-40.			
	C63	LARSEN, C.P., et al., "Long-term acceptance of skin and cardiac allografts after blocking CD40 and CD28 pathways," Nature. 1996 May 30;381(6581):434-8.			
	C64	LINKER-ISRAELI M, et al., "CD8+ lymphocytes from patients with systemic lupus erythematosus sustain, rather than suppress, spontaneous polyclonal IgG production and synergize with CD4+ cells to support autoantibody synthesis." Arthritis Rheum. 1990 Aug;33(8):1216-25.			
	C65	LUCAS et al., "The development of cellular immunity to Epstein-Barr virus after allogeneic bone marrow transplantation", Blood 87:2594-2603 (1996)			
	C66	MARTIN et al., "Effects of in vitro depletion of T cells in HLA-identical allogeneic marrow grafts", Blood 66:664-672 (1985)			
	C67	MARTIN et al., "Effects of treating marrow with a CD3-specific immunotoxin for prevention of acute graft-versus-host disease", Bone Marrow Transplant 3:437-444 (1989)			
	C68	MARTIN, "Overview of Marrow Transplantation Immunology", in Bone Marrow Transplantation (eds. Forman et al.) pp. 16-21, Boston, Blackwell Scientific Publications (1994)			
	C69	MARTIN, P.J. et al., "Treatment of Acute Graft-Versus-Host Disease with Anti-CD3 Monoclonal Antibodies," Am Jour Kidney Disease 11(2):149-152 (1988)			
	C70	MASSAGUE J., "The transforming growth factor-beta family." Annu Rev Cell Biol. 1990;6:597-641.			
	C71	MASSAGUE, "Receptors for the TGF-beta family", Cell 69:1067-1070 (1992)			
	C72	MIZUOCHI, T., et al., "Both L3T4+ and Lyt-2+ helper T cells initiate cytotoxic T lymphocyte responses against allogeneic major histocompatibility antigens but not against trinitrophenyl-modified self," J Exp Med. 1985 Aug 1;162(2):427-43.			
	C73	MORRIS, "Prevention and treatment of allograft rejection in vivo by rapamycin: molecular and cellular mechanisms of action", Ann NY Acad Sci 685:68-72 (1993)			
	C74	MURPHY et al, "The potential role of NK cells in the separation of graft-versus-tumor effects from graft-versus-host disease after allogeneic bone marrow transplantation," Immunol Rev 157:167-176 (1997)			
	C75	MYSLIWETZ J and THIERFELDER S., "Antilymphocytic antibodies and marrow transplantation. XII. Suppression of graft-versus-host disease by T-cell-modulating and depleting antimouse CD3 antibody is most effective when preinjected in the marrow recipient." Blood. 1992 Nov 15;80(10):2661-7 (Abstract)			
	C76	OHTSUKA, K., et al., "Decreased Production of TGF-beta by Lymphocytes from Patients with Systemic Lupus Erythematosus", J. Immunol. 160:2539-2545 (1998).			
	C77	OSWALD, et al., "IL-10 Synergizes with IL-4 and Transforming Growth Factor-Beta to Inhibit macrophage Cytotoxic Activity," J Immunology 148(11):3578-3582 (1992)			

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible.

<sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1118358\_1.DOC

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				<b>Complete if Known</b>	
				Application Number	To Be Assigned
				Filing Date	Herewith
				First Named Inventor	HORWITZ, David A.
				Group Art Unit	
				Examiner Name	
Sheet	6	of	8	Attorney Docket Number	A-67279-8/RFT/RMS/RMK (469443-63)

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS					
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.			
	C78	PAPIERNIK M, et al., "T cell deletion induced by chronic infection with mouse mammary tumor virus spares a CD25-positive, IL-10-producing T cell population with infectious capacity." J Immunol. 1997 May 15;158(10):4642-53.			
	C79	PATTERSON et al., "Graft rejection following HLA matched T-lymphocyte depleted bone marrow transplantation", Br J Haematol 63:221-230 (1986)			
	C80	PAWELEC, et al., "Cytokine Modulation of TH1/TH2 Phenotype Differentiation in Directly Alloresponsive CD4+ Human T Cells," Transplantation 62(8):1095-1101 (1996)			
	C81	PEARCE, N.W., et al., "Specific unresponsiveness in rats with prolonged cardiac allograft survival after treatment with cyclosporine. V. Dependence of CD4+ suppressor cells on the presence of alloantigen and cytokines, including interleukin 2," Transplantation. 1993 Feb;55(2):374-80.			
	C82	PESCOVITZ, M.D., et al., "Effect of class II antigen matching on renal allograft survival in miniature swine," J Exp Med. 1984 Nov 1;160(5):1495-508. QIN, L., et al., "Gene transfer for transplantation. Prolongation of allograft survival with transforming growth factor-beta 1," Ann Surg. 1994 Oct;220(4):508-18; discussion 518-9.			
	C83	POWRIE F, et al., "A critical role for transforming growth factor-beta but not interleukin 4 in the suppression of T helper type 1-mediated colitis by CD45RB(low) CD4+ T cells." J Exp Med. 1996 Jun 1;183(6):2669-74.			
	C84	QIN, L., et al., "Gene transfer for transplantation. Prolongation of allograft survival with transforming growth factor-beta 1," Ann Surg. 1994 Oct;220(4):508-18; discussion 518-9			
	C85	QIN, L., et al., "Retrovirus-mediated transfer of viral IL-10 gene prolongs murine cardiac allograft survival," J Immunol. 1996 Mar 15;156(6):2316-23.			
	C86	RAJU, G.P., et al., "Prolongation of cardiac allograft survival with transforming growth factor-beta 1 in rats," Transplantation. 1994 Aug 15;58(3):392-6.			
	C87	RAMSDELL, F. and FOWLKES, B.J., "Maintenance of in vivo tolerance by persistence of antigen," Science. 1992 Aug 21;257(5073):1130-4.			
	C88	READ S, et al., "Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of CD25(+)CD4(+) regulatory cells that control intestinal inflammation." J Exp Med. 2000 Jul 17;192(2):295-302.			
	C89	ROCHA, B., et al., "Clonal anergy blocks in vivo growth of mature T cells and can be reversed in the absence of antigen," J Exp Med. 1993 May 1;177(5):1517-21.			
	C90	RODT, H., "Anti-lymphocytic antibodies and marrow transplantation. 3. Effect of heterologous anti-brain antibodies on acute secondary disease in mice", Eur. J. Immunol 4:25-29 (1974)			
	C91	ROOK et al., "Effects of Transforming Growth Factor on the Functions of Natural Killer Cells: Depressed Cytolytic Activity and Blunting of Interferon Responsiveness," J Immunology 136(10):3916-3920 (1986)			
	C92	ROSER, B.J., "Cellular mechanisms in neonatal and adult tolerance," Immunol Rev. 1989 Feb;107:179-202.			
	C93	SAKAGUCHI S, et al., "Organ-specific autoimmune diseases induced in mice by elimination of T cell subset. I. Evidence for the active participation of T cells in natural self-tolerance; deficit of a T cell subset as a possible cause of autoimmune disease." J Exp Med. 1985 Jan 1;161(1):72-87.			
	C94	SAKAGUCHI, S., et al., "Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases," J Immunol. 1995 Aug 1;155(3):1151-64.			

Examiner Signature	Date Considered
--------------------	-----------------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible.

<sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1118358\_1.DOC



Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)			<b>Complete if Known</b>		
			Application Number	To Be Assigned	
			Filing Date	Herewith	
			First Named Inventor	HORWITZ, David A.	
			Group Art Unit		
			Examiner Name		
Sheet	7	of	8	Attorney Docket Number	A-67279-8/RFT/RMS/RMK (469443-63)

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		
	C95	SEDDON, B. and MASON, D., "The third function of the thymus," Immunol Today. 2000 Feb;21(2):95-9.		
	C96	SHEVACH, E.M., "Regulatory T cells in autoimmunity," Annu Rev Immunol. 2000;18:423-49.		
	C97	SHIVAKUMAR S, et al., "T cell receptor alpha/beta expressing double-negative (CD4-/CD8-) and CD4+ T helper cells in humans augment the production of pathogenic anti-DNA autoantibodies associated with lupus nephritis." J Immunol. 1989 Jul 1;143(1):103-12.		
	C98	SINGER, A., et al., "Self recognition in allogeneic radiation bone marrow chimeras. A radiation-resistant host element dictates the self specificity and immune response gene phenotype of T-helper cells," J Exp Med. 1981 May 1;153(5):1286-301.		
	C99	SNIJDEWINT, F.G., et al., "Prostaglandin E2 differentially modulates cytokine secretion profiles of human T helper lymphocytes," J Immunol. 1993 Jun 15;150(12):5321-9.		
	C100	SPORN et al., "Some recent advances in the chemistry and biology of transforming growth factor-beta," J Cell Biol 105:1039-1045 (1987)		
	C101	STARZL, T.E., et al., "Chimerism and donor-specific nonreactivity 27 to 29 years after kidney allotransplantation," Transplantation. 1993 Jun;55(6):1272-7.		
	C102	STORB et al., "Long-term follow-up of a controlled trial comparing a combination of methotrexate plus cyclosporine with cyclosporine alone for prophylaxis of graft-versus-host disease in patients administered HLA-identical marrow grafts for leukemia", Blood 80:560-561 (1992)		
	C103	STRAND, V., "Approaches to the management of systemic lupus erythematosus," Current Opinion in Rheumatology, 9:410-420 (1997)		
	C104	SULLIVAN et al., "Chronic Graft-Versus-Host Disease and Other Late Complications of Bone Marrow Transplantation", Semin Hematol 28:250-259 (1992)		
	C105	SURI-PAYER E, et al., "CD4+CD25+ T cells inhibit both the induction and effector function of autoreactive T cells and represent a unique lineage of immunoregulatory cells." J Immunol. 1998 Feb 1;160(3):1212-8.		
	C106	SURI-PAYER E, et al., "Post-thymectomy autoimmune gastritis: fine specificity and pathogenicity of anti-H/K ATPase-reactive T cells." Eur J Immunol. 1999 Feb;29(2):669-77.		
	C107	SYKES, M. et al., "In Vitro And In Vivo Analysis Of Bone Marrow-Derived CD3+, CD4-, CD8-, NK1.1+ Cell Lines," Cell Immunol. 129(2):478-93 (1990)		
	C108	TAAMS, L.S., et al., "Anergic T cells actively suppress T cell responses via the antigen-presenting cell," Eur J Immunol. 1998 Sep;28(9):2902-12.		
	C109	TAKAHASHI T, et al., "Human CD8+ lymphocytes stimulated in the absence of CD4+ cells enhance IgG production by antibody-secreting B cells." Clin Immunol Immunopathol. 1991 Mar;58(3):352-65.		
	C110	TAKAHASHI T, et al., "Immunologic self-tolerance maintained by CD25+CD4+ naturally anergic and suppressive T cells: induction of autoimmune disease by breaking their anergic/suppressive state." Int Immunol. 1998 Dec;10(12):1969-80.		
	C111	TAYLOR, "Antigen specific suppressor T cells respond to cytokines released by T cells", Advances Exp Med Biol 319:125-135 (1992)		
	C112	THORNTON AM and SHEVACH EM. "CD4+CD25+ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin 2 production." J Exp Med. 1998 Jul 20;188(2):287-96.		
Examiner Signature			Date Considered	

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1118358\_1.DOC

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO (Modified)  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				<b>Complete if Known</b>		
				Application Number	To B Assign d	
				Filing Date	H rewith	
				First Named Inventor	HORWITZ, David A.	
				Group Art Unit		
Examiner Name						
Attorney Docket Number	A-67279-8/RFT/RMS/RMK (469443-63)					
Sheet	8	of	8			

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS					
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.			
	C113	THORNTON AM and SHEVACH EM. "Suppressor effector function of CD4+CD25+ immunoregulatory T cells is antigen nonspecific." J Immunol. 2000 Jan 1;164(1):183-90.			
	C114	TOMITA, Y., et al., "Importance of suppressor T cells in cyclophosphamide-induced tolerance to the non-H-2-encoded alloantigens. Is mixed chimerism really required in maintaining a skin allograft tolerance?" J Immunol. 1990 Jan 15;144(2):463-73.			
	C115	VALLERA et al., "Bone marrow transplantation across major histocompatibility barriers in mice. Effect of elimination of T cells from donor grafts by treatment with monoclonal Thy-1.2 plus complement or antibody alone", Transplantation 31:218-222 (1981)			
	C116	VENDETTI, S., et al., "Anergic T cells inhibit the antigen-presenting function of dendritic cells," J Immunol. 2000 Aug 1;165(3):1175-81.			
	C117	VERBANAC, K.M., et al., "A role for transforming growth factor-beta in the veto mechanism in transplant tolerance," Transplantation. 1994 Mar 27;57(6):893-900.			
	C118	VIA et al., "Critical Role of interleukin-2 in the development of acute graft-versus-host disease", International Immunol 5:565-572 (1993)			
	C119	WAHL SM. "Transforming growth factor beta: the good, the bad, and the ugly." J Exp Med. 1994 Nov 1;180(5):1587-90.			
	C120	WEINER HL, et al., "Oral tolerance: immunologic mechanisms and treatment of animal and human organ-specific autoimmune diseases by oral administration of autoantigens." Annu Rev Immunol. 1994;12:809-37			
	C121	WEKERLE, T., et al., "Anti-CD154 or CTLA4lg obviates the need for thymic irradiation in a non-myeloablative conditioning regimen for the induction of mixed hematopoietic chimerism and tolerance," Transplantation. 1999 Nov 15;68(9):1348-55.			
	C122	WILSON, D.B., "Idiotypic regulation of T cells in graft-versus-host disease and autoimmunity," Immunol Rev. 1989 Feb;107:159-77.			
	C123	ZEHAVI-WILLNER et al., "The Mitogenic Activity of Staphylococcal Enterotoxin B (SEB): A Monovalent T Cell Mitogen That Stimulates Cytolytic T Lymphocytes but Cannot Mediate Their Lytic Interaction," Journal of Immunology 127(8):2682-2687 (1986)			
	C124	ZELLER et al., "Induction of CD4+ T Cell Alloantigen-Specific Hyporesponsiveness by IL-10 and TGF- 1, Journal of Immunology 163:3684-3691 (1999)			
	C125	ZELLER, et al., "Ex vivo IL10 and TGF-Beta Act Synergistically to Induce CD4+ Alloantigen-Specific Tolerance Resulting in Diminished Graft-Versus-Host Disease in Vivo," FASEB Journal (March 12, 1999) 12(4)part 1, A614. Meeting Info: Annual Meeting of the Professional Research Scientists for Experimental Biology. April 17-21 1999			
	C126	ZHENG, X.X., et al., "Administration of noncytolytic IL-10/Fc in murine models of lipopolysaccharide-induced septic shock and allogeneic islet transplantation," J Immunol. 1995 May 15;154(10):5590-600.			

Examiner Signature	Date Considered
--------------------	-----------------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible.

<sup>6</sup> Applicant is to place a check mark here if English Language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 1118358\_1.DOC